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Preventing hemorrhage in high-risk hemodialysis: Regional versus low-dose heparin

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Preventing hemorrhage in high-risk hemodialysis: Regional versus low-dose heparin. Hemodialysis in patients with increased risk for hemorrhage can be accomplished with either a regional or a low, total dose of heparin. In a prospective study of 69 series of dialyses performed on an alternating schedule of heparinization for each patient, bleeding complications during and immediately following dialysis occurred in 23 of 122 dialyses (19%) with regional heparin compared to 13 of 133 dialyses (10%) with low-dose heparin ($P < 0.05$). The incidence of hemorrhage correlated with the estimated degree of bleeding risk both at expected and at occult bleeding sites, and was the same or higher with regional heparin in all categories. Hemorrhage was not correlated with preexisting coagulation abnormalities, concurrent anticoagulant drugs, level of azotemia, or ability to successfully limit systemic heparinization during dialysis. The incidence of partial clotting of the dialyzer was 3 to 5% with both heparin protocols. We conclude that regional heparinization has no clinical or practical advantage over low-total-dose heparin in preventing bleeding associated with hemodialysis.

Prévention de l'hémorragie au cours de l'hémodialyse à haut risque: Héparinisation régionale ou héparinisation à faibles doses. L'hémodialyse des malades dont le risque hémorragique est élevé peut être réalisée soit avec une héparinisation régionale soit avec une dose totale faible d'héparine. Au cours d'une étude prospective portant sur 69 séries de dialyses réalisées selon un protocole où les modes d'héparinisation étaient alternés chez chaque malade, les complications hémorragiques au cours et au décours immédiat de la dialyse ont été observées dans 23 dialyses sur 122 (19%) conduites avec une héparinisation régionale et 13 dialyses sur 133 (10%) réalisées avec une faible dose d'héparine ($P < 0,05$). La fréquence des hémorragies était corrélée avec l'évaluation du risque de saignement et elle a été la même ou plus grande lors de l'héparinisation régionale. L'hémorragie n'a pas été corrélée avec les anomalies pré-existantes de la coagulation, les traitements anticoagulants, l'importance de l'azotémie ou la possibilité de limiter efficacement l'héparinisation au cours de la dialyse. La fréquence de la coagulation partielle dans le dialyseur a été de 3 à 5% avec l'un et l'autre des protocoles. Nous concluons que l'héparinisation régionale n'a d'advantage ni clinique, ni pratique sur l'utilisation d'une dose totale faible d'héparine dans la prévention du saignement associé à l'hémodialyse.

Anticoagulation with heparin is necessary during hemodialysis to prevent clotting in the extracorporeal circulation. For patients with increased risk of bleeding, two major modes of heparinization have been used that achieve a level of anticoagulation adequate to prevent extracorporeal clotting while limiting the systemic anticoagulation of the patient. One method is "regional" anticoagulation during hemodialysis, which involves infusion of heparin into the blood entering the dialyzer, and neutralization by infusion of protamine into the heparinized blood as it returns to the patient [1–3]. To avoid bleeding complications from a delayed heparin effect, additional administration of protamine several hours after dialysis has been suggested [4]. Theoretically, this method avoids detectable systemic anticoagulation of the patient; regional heparinization, however, is not used widely because of the technical difficulties in determining proper infusion rates of heparin and protamine to achieve extracorporeal and avoid systemic anticoagulation. The other method of limited anticoagulation involves low-dose, tightly controlled heparinization without protamine, as has been proposed recently [5–7]. This method is much simpler, as it requires monitoring of only extracorporeal anticoagulation and adjustment of the heparin dose.

Reproducible regional heparinization has been the procedure of choice in our institution for the past several years. In spite of good procedural control, however, severe bleeding continues to be a cause of serious morbidity in patients at risk. In view of the lack of detailed comparative studies, we designed this prospective study to compare the efficacy of regional heparinization with that of limited-dose, systemic heparinization in preventing both

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dialyzer clotting and bleeding complications in patients with high risk for hemorrhage.

Methods

Regional heparinization (RH) was performed by the method of Spencer et al [8] monitoring heparin therapy with at least 0.5 hourly thrombin clotting times (TCT) [9, 10]. Heparin (Panheprin, Abbott Laboratories, N. Chicago, Illinois; or Lipo-Hepin, Riker Laboratories, Inc., Northridge, California) was infused into blood before it entered the dialyzer at a rate calculated to attain a level of 0.3 U of heparin/ml. Protamine (Protamine Sulfate Injection, U.S.P., Eli Lilly and Company, Indianapolis, Indiana) infused into blood leaving the dialyzer was estimated at approximately 1 mg of protamine per 100 U heparin and was adjusted to keep the TCT of the blood returning to the patient near baseline. An additional dose of 50 mg of protamine was given i.v. 3 hours after dialysis. Low-total-dose heparinization (LTH) was performed by intravenous loading with 5 to 10 U heparin/lb of body wt, and then infusing heparin continuously at a rate of 10 U/lb of body wt/hr into the blood flowing from the patient into the dialyzer. Changes in heparin infusion rate and/or additional small doses of heparin were given to maintain the extracorporeal TCT at 2 to 3 times baseline.

Patients were selected for the present study prospectively. All patients in our hemodialysis unit who required limited heparinization because of bleeding risk between November 1977 and July 1978 were included. Consecutive patients were assigned alternately to two groups: in either group, serial dialysis treatments during the period of bleeding risk were each performed with RH or LTH on an alternating schedule; in one group, patients began the alternating schedule with RH and in the other group with LTH. With this design, RH and LTH were distributed with approximately equal frequency across various degrees of bleeding risk, various clinical settings, and specific sites of bleeding risk, and various intervals into the time-course of bleeding risk. All dialyses lasted 3.5 to 5.0 hours and were performed via arteriovenous shunt or two needles, one of which might be a femoral vein catheter. The Cordis Dow hollow-fiber artificial kidney, with surface area of 1.3 to 2.5 m^2, was used in this study because the noncompliant blood volume of this dialyzer allowed estimation of the degree of dialyzer clotting from the reduction in this volume after dialysis [11]. The blood flow rates averaged 200 to 210 ml/min among all dialyses in each heparinization protocol.

Bleeding risk was prospectively assessed in all patients prior to each dialysis. Risk was categorized as follows: "very high risk" as active bleeding at the time of dialysis; "high risk" as active bleeding now stopped for less than 3 days, surgical or traumatic wounds within the previous 3 days, or acute dialysis via temporary femoral vein catheter (with a separate site for blood return); "moderate risk" as active bleeding now stopped for more than 3 but less than 7 days, surgical or traumatic wounds of 3 to 7 days duration, or the presence of uremic pericarditis; and "low risk" as more than 7 days beyond any active bleeding or surgical or traumatic injury. These risk assessments applied only to a specific bleeding site, denoted hereafter as the "primary" site, which was the basis for both a special heparinization procedure as well as for inclusion in the study. Bleeding also occurred at unexpected or unknown sites, and these were denoted as "secondary" sites.

Detection of bleeding complications was based on observation of bleeding or on serial determinations of hematocrit. Observation of gross bleeding at a primary or secondary site was considered as a definite complication if it occurred during dialysis, and as a probable complication if it occurred during the 24 hours following dialysis. The present study did not consider minor bleeding complications such as subconjunctival hemorrhage or minor venipuncture bleeding at the dialysis fistula. Occult bleeding (for example, gastrointestinal, retroperitoneal) was judged to have occurred in the following circumstances: *(a)* a fall in hematocrit of 3 vol% or more during dialysis confirmed by a repeat determination at 12 to 24 hours following dialysis; *(b)* a fall in hematocrit of 3 vol% or more in the 24 hours following dialysis verified by a repeat hematocrit at 24 to 48 hours following dialysis; and *(c)* any decrease in hematocrit despite either blood transfusion or weight loss of more than 5 lb during dialysis, verified by a subsequent hematocrit measurement. A second review of the case records was carried out to eliminate any cases with unconfirmed hematocrit changes, complications that did not represent a change in the course of previous bleeding, and some other cause of decline in hematocrit, such as hemolysis.

All patients studied had the following additional determinations: *(a)* predialysis and postdialysis BUN, platelet count, prothrombin time, and partial thromboplastin time; *(b)* individual predialysis in vitro response to heparin at a concentration of 0.3 U/ml whole blood, as described by Spencer et al [8]; *(c)* residual volume capacity of the dialyzer blood

compartment after dialysis to estimate the extent of coagulation in the apparatus [11]; and *(d)* changes in vital signs and weight, and recording of all medication with an effect on coagulation factors, platelet function, or hematocrit.

Statistical analysis of data included Student's *t* test to compare mean values between groups, and the χ^2 test to compare frequency of various factors between groups.

Results

A total of 69 courses of alternating RH and LTH dialyses, varying in length from one to nine treatments, was studied in 59 patients. Seven patients entered the study more than one time during the 8-month period. Four patients with bleeding risk requiring hemodialysis had to be excluded because of the use of single-needle dialysis or a dialyzer other than the hollow-fiber artificial kidney. Equivalent numbers of dialyses were performed in the setting of acute and chronic renal failure. Specific clinical diagnoses necessitating the use of limited heparinization among the 255 dialyses studied included: surgery or trauma in 205 dialyses, gastrointestinal bleeding in 38 dialyses, genitourinary bleeding in 34 dialyses, pericarditis in 45 dialyses, and femoral vein or artery catheterization in 48 dialyses. It should be noted that in 25 of 45 dialyses during pericarditis and in 33 of 48 dialyses with femoral vessel catheterization, there was more than one indication for limited heparinization.

Table 1. Distribution of dialyses and complications according to risk and heparinization protocol

Bleeding risk	*N*	Protocol[b]	Bleeding complications[a]		
			During dialysis	Within 24 hr after dialysis	Total
Very high	15	RH	3 (20%)	4 (27%)	7 (47%)
	16	LTH	3 (19%)	3 (19%)	6 (38%)
High	48	RH	5 (10%)	6 (13%)	11 (23%)
	47	LTH	2 (4%)	3 (6%)	5 (11%)
Moderate	42	RH	2 (5%)	3 (7%)	5 (12%)
	53	LTH	1 (2%)	1 (2%)	2 (4%)
Low	17	RH	0 (0%)	0 (0%)	0 (0%)
	17	LTH	0 (0%)	0 (0%)	0 (0%)
Total	122	RH	10 (8%)	13 (11%)	23 (19%)[c]
	133	LTH	6 (5%)	7 (5%)	13 (10%)[c]

[a] Absolute number (percentage)
[b] RH is regional heparin; LTH, low-total-dose heparin.
[c] $P < 0.05$, comparing total RH to total LTH for all complications.

Table 2. Site of bleeding complications[a]

Bleeding risk	*N*	Protocol	Primary site	Secondary site
Very high	15	RH	3	4
	16	LTH	4	2
High	48	RH	3	8
	47	LTH	1	4
Moderate	42	RH	0	5
	53	LTH	0	2
Low	17	RH	0	0
	17	LTH	0	0
Total	122	RH	6	17[b]
	133	LTH	5	8[b]

[a] Abbreviations are defined in Table 1.
[b] $P < 0.05$ comparing RH to LTH.

As shown in Table 1, the 255 dialyses included in this study were comparably distributed between RH and LTH protocols and among different degrees of bleeding risk. Overall, the consecutive and alternating design of this study accomplished the objective of distributing dialyses similarly between heparinization protocols, degrees of risk and clinical settings.

Analysis of bleeding complications, also shown in Table 1, revealed that patients with very high risk had worsened bleeding during or following dialysis with both RH and LTH, and that there was no significant advantage of one heparinization scheme over the other in this risk group. The incidence of bleeding decreased as the risk decreased in both RH and LTH dialyses, but bleeding tended to be more frequent with RH than it did with LTH in both the high and moderate risk dialyses ($P < 0.10$). Overall, the incidence of hemorrhage was significantly greater among all RH than it was among all LTH dialyses.

Assigned bleeding risk always referred to a specific site of potential bleeding. The bleeding complication, however, frequently did not occur at the primary site, as shown in Table 2. Occult or unexpected bleeding episodes at secondary sites tended to be more frequent with RH dialysis in all risk categories, and the total number of bleeding complications at secondary sites was significantly greater with RH than it was with LTH ($P < 0.05$).

Factors which could predispose patients to bleeding are shown in Table 3. Coagulation abnormalities, defined as an abnormality in two or more parameters (TCT, prothrombin time, partial thromboplastin time, and platelet count), commonly related to the complicated nature of our patients' underlying illnesses, but did not correlate with the development of bleeding complications. Administration of concurrent anticoagulant therapy, such as low-dose heparin and antiplatelet drugs, was not associated with bleeding complications and was not read-

ily detectable by routine coagulation testing. The total heparin dose administered during dialysis did not differ between patients with and without bleeding complications in either the RH or LTH groups. The total heparin dose during RH, however, was four to five times higher than that during LTH, and the dose of protamine averaged 1 mg/100 U of heparin during RH. Finally, the degree of azotemia before dialysis was similar in both dialysis groups and did not correlate with bleeding complications.

Control of systemic heparinization during both protocols is described in Table 4. The maximum systemic TCT, a measure of the maximum heparinization of the patient, remained on the average less than 50% of the TCT for a heparin concentration of 0.3 U/ml during all RH dialyses, and did not differ significantly between RH dialyses with or without bleeding complications. Control of LTH procedures was achieved on the average with a maximum systemic TCT approximating the TCT for a heparin concentration of 0.3 U/ml, and no statistical difference between LTH dialyses with or without bleeding complications. Therefore, RH was associated with a higher rate of bleeding complications than was LTH, even though both protocols succeeded in controlling systemic heparinization as designed.

Dialyzer clotting during RH and LTH protocols was estimated by the incidence of marked loss in dialyzer volume during dialysis [11]. The maximum volume loss during this study was 60%, and sufficient clotting to reduce dialyzer volume by 30% or more of the original volume occurred in 3% of RH and 5% of LTH dialyses as shown in Table 5. The degree of anticoagulation in the dialyzer, determined by the TCT in extracorporeal blood entering the dialyzer, ranged from a low value of about twice the baseline TCT to a high of well above the TCT for a heparin concentration of 0.3 U/ml in both the RH and the LTH groups (Tables 4 and 5). Both the maximum and minimum extracorporeal TCT values were significantly lower in RH dialyses with clotting than they were in RH dialyses without marked clotting. These data suggest that dialyzer clotting is uncommon with either protocol. Furthermore, dialyzer clotting during RH dialysis is associated with lesser degrees of extracorporeal heparinization, implying that the large doses of heparin used are necessary to prevent this clotting. Shunt clotting occurred only once during dialysis and was probably related to local factors rather than to the heparinization procedure.

Discussion

The bleeding patient who has renal failure requiring hemodialysis presents the clinical dilemma of balancing the risk of increased bleeding against the need to prevent dialyzer clotting with heparin thera-

Table 3. Relation of bleeding complications to possible predisposing factors[a]

	RH		LTH	
	Bleeding (N = 23)	No bleeding (N = 99)	Bleeding (N = 13)	No bleeding (N = 120)
Preexisting coagulation abnormality[b]	7 (30%)	26 (26%)	3 (23%)	28 (23%)
Concurrent anticoagulant drugs[b]	5 (22%)	12 (13%)	4 (31%)	17 (15%)
Total heparin dose[c]	176 ± 15	202 ± 8	44 ± 5	47 ± 2
BUN[c]	95 ± 9	85 ± 4	100 ± 15	86 ± 3

[a] Abbreviations are defined in Table 1. There is no significant difference, for any parameters, between "bleeding" and "no bleeding" in RH or in LTH.
[b] Absolute number (percentages).
[c] Values are means ± SEM; total heparin dose is in U/lb body wt and BUN is in mg/100 ml.

Table 4. Control of systemic anticoagulation during dialysis[a]

	RH		LTH	
	Bleeding (N = 23)	No bleeding (N = 99)	Bleeding (N = 13)	No bleeding (N = 120)
Baseline TCT, *sec*	9.3 ± 0.3	9.3 ± 0.3	9.7 ± 0.3	9.6 ± 0.1
Maximum systemic TCT, *sec*	13.1 ± 2.1	11.4 ± 0.6	32.0 ± 6.6	27.0 ± 1.7
TCT at 0.3 U heparin/ml blood, *sec*	30.0 ± 4.2	26.0 ± 1.8	25.0 ± 3.5	30.0 ± 1.4

[a] There is no significant difference, for any parameters, between "bleeding" and "no bleeding" in RH or in LTH. TCT is thrombin clotting time; other abbreviations are defined in Table 1. Values are means ± SEM.

Table 5. Dialyzer clotting during dialysis[a]

	RH		LTH	
	Clotting ($N = 4$)	No clotting ($N = 118$)	Clotting ($N = 7$)	No clotting ($N = 126$)
Extracorporeal TCT, *sec*				
Maximum	38 ± 6[b]	72 ± 3[b]	58 ± 11	59 ± 2
Minimum	17 ± 2[c]	24 ± 2[c]	20 ± 3	17 ± 1

[a] There is no significant difference in frequency of clotting between RH and LTH. Abbreviations are defined in Tables 1 and 4. Values are means ± SEM.

[b] $P < 0.001$, comparing high TCT between clotting and no clotting.

[c] $P < 0.01$, comparing low TCT between clotting and no clotting.

py. Advocates for either limited-total-dose heparinzation [5–7, 12] or regional heparinization [1–3, 8, 13] have reported their experience, but no detailed prospective comparison has been presented to date. Because each method has theoretical advantages, and because regional heparinization is technically more difficult to perform, it is of great clinical and practical importance to determine the comparative success of these procedures in achieving the optimal balance between bleeding risk and extracorporeal anticoagulation.

The data presented here clearly show that well-controlled regional heparinization is not superior to closely monitored limited-dose heparinization in the very high-risk patient with active hemorrhage at the time of dialysis. Furthermore, regional heparinization may be associated with a higher incidence of hemorrhage from expected and unexpected sites in all patients with increased risk for bleeding.

Several factors may be responsible for this finding. *(a)* The dose of heparin required to maintain adequate regional heparinization is high [1, 2, 8] because heparin is neutralized on each pass out of dialyzer back to the patient. Constant infusion of at least 4000 U of heparin/hr is required to maintain a heparin concentration of 0.2 to 0.3 U/ml at a dialyzer blood flow rate of 200 to 300 ml/min. *(b)* It is possible that difficulty in controlling systemic heparinization or unpredictable patient-responsiveness to heparin [14, 15] could account for the rate of bleeding complications in our RH patients. Data shown in Table 4, however, indicate that neither systemic over-heparinization nor in vitro evidence of increased heparin responsiveness was associated with bleeding complications in this study. *(c)* The fate of the heparin-protamine complex in vivo is not understood well, and the phenomenon of "heparin rebound" associated with protamine has been implicated in delayed bleeding after dialysis [4, 16]. As a result, most protocols, like our own, have included a late dose of protamine to prevent heparin rebound. *(d)* It is also possible that protamine itself may be responsible for some bleeding complications [17]; the occurrence, however, of more frequent bleeding complications during as well as after RH, compared to LTH, suggest that late protamine is not the only cause of frequent bleeding in the RH protocol. *(e)* Two important consequences of heparin therapy may be platelet loss [18–21] and an effect of high doses on platelet function [22–24]. In uremic patients, any decrease in platelet number or function would further compromise hemostatic mechanisms and predispose to bleeding.

Regional heparinization might possibly be designed to achieve fewer bleeding complications through development of protocols using lower doses. Yet any regional protocol would still necessitate the use of additional equipment, higher doses of heparin and protamine, and added coagulation tests. Therefore, practical considerations, combined with data presented here on bleeding complications, make limited-dose systemic heparinization the preferred method in all hemodialysis patients with risk for bleeding. In extreme circumstances of life-threatening hemorrhage, peritoneal dialysis remains a possible alternative because heparinization is not required for this procedure. In many cases with thoracic or abdominal disease, however, peritoneal dialysis is difficult to perform and hemodialysis is necessary.

Our observations for hemorrhage in the 24 hours after dialysis and at unexpected sites may explain our high incidence of hemorrhage compared to recent reports concerning patients at risk [5–7]. In fact, the 10 to 19% incidence in the present study is comparable to that originally reported by Maher et al in their original experience with regional heparinization [2]. Our data suggest that uremic patients with a known bleeding risk also have a propensity to hemorrhage from other sites, emphasizing the need for careful observation for blood loss after as well as during dialysis, and from occult as well as expected locations.

In summary, low-total-dose heparinization is at least as effective as regional heparinization in limiting both clotting in the dialyzer and hemorrhagic complications in renal failure patients with increased bleeding risk. The lower cost, technical advantages, and clinical efficacy make low-total-dose heparinization the preferable mode of anticoagulation in patients who require hemodialysis while at risk of bleeding.

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